Immunogenicity and Safety of DTaP5-IPV-HepB-Hib (Vaxelis™), a Pediatric Hexavalent Combination Vaccine

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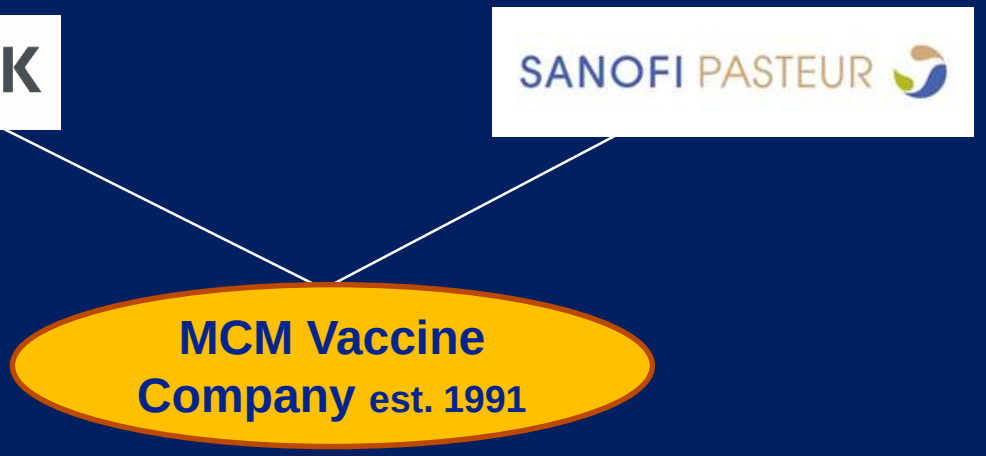
Benefits of Combination Vaccines

- Comprised of licensed components
- Implementation has helped reduce number of injections and confusion in childhood vaccination schedule [1,2,3]
- Have been shown to improve vaccination compliance and timeliness [1,2,3]
  - On time vaccination rates increased with use of higher-valent combination vaccines [1,2,3]
  - Missed or delayed vaccinations put children at risk and increase likelihood of infection [3,4,5]
- Have been shown to improve office visit efficiency [6,7]
  - May reduce need for additional office visits to achieve full vaccination status [7]
  - May reduce vaccine preparation time and administrative tasks [6,7]
  - Can allow for more time to be spent on patient care [6]

1. Kalies H et al. *Pediatr Infect Dis J* 2006;25(6):507-512; 2. Marshall GS et al. *Pediatr Infect Dis J* 2007; 26(6):496-500; 3. Happe LE et al. *Am J Manag Care* 2007; 13(9):506-512; 4. Glanz JM et al. *JAMA Pediatr*. 2013;167(11):1060-1064; 5. Omer SB et al. *N Engl J Med* 2009;360(19): 1981-1988; 6. Pellissier JM et al. *Am J Manag Care* 2000;6(9):1038-1044; 7. Goldfarb NI et al. *Managed Care* 2005; 14(6 Suppl):3-12

A Joint Venture Between Two Companies



Governance			
Manufacture	HepB, Hib	+	DTaP5, IPV Formulation, Release
Development	Clinical Lead	+	Partner
	Partner	+	Regulatory Lead
Co-Promotion	Merck	+	Sanofi Pasteur
Pharmacovigilance	Lead Holds global safety database	+	Partner

Vaxelis™ : Comprised of Licensed Components

Antigen(s)		Amounts in hexavalent vaccine	Licensed vaccine containing the same antigen(s)
MERCK	**PRP-OMPC** **Polyribosylribitol phosphate polysaccharide coupled to the outer membrane protein complex of *Neisseria meningitidis***	**3 µg**	**PEDVAX HIB®**
	HBsAg **Recombinant hepatitis B surface antigen**	**10 µg**	**RECOMBIVAX HB®**
SANOFI PASTEUR	**5 component acellular pertussis** **• PT: Pertussis Toxoid** **• FHA: Filamentous Hemagglutinin** **• PRN: Pertactin** **• FIM: Fimbriae Types 2 and 3** **Diphtheria Toxoid** **Tetanus Toxoid**	 **20 µg** **20 µg** **3 µg** **5 µg** **15 Lf (≥20 IU)** **5 Lf (≥40 IU)**	**DAPTACEL®** **PENTACEL®**
	IPV - Inactivated Poliovirus **• Type 1** **• Type 2** **• Type 3**	 **29-DU** **7-DU** **26-DU**	 **IPOL®**

Aluminium (0.319 mg) used as adjuvant

Fully liquid formulation requires no reconstitution, simplifying administration

Vaxelis: Indication and Schedule (USPI)

1 INDICATIONS AND USAGE

VAXELIS is a vaccine indicated for active immunization to prevent diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *Haemophilus influenzae* (*H. influenzae*) type b. VAXELIS is approved for use as a 3-dose series in children 6 weeks through 4 years of age (prior to the 5th birthday).

2.1 Vaccination Schedule

VAXELIS is to be administered as a 3-dose series at 2, 4, and 6 months of age. The first dose may be given as early as 6 weeks of age. Three doses of VAXELIS constitute a primary immunization course against diphtheria, tetanus, *H. influenzae* type b invasive disease and poliomyelitis.

VAXELIS may be used to complete the hepatitis B immunization series.

A 3-dose series of VAXELIS does not constitute a primary immunization series against pertussis; an additional dose of pertussis-containing vaccine is needed to complete the primary series.

Hib Antigen Amount in Final Vaxelis Formulation Based on Phase II Hexavalent Vaccine (HV) Results

	Postdose 3 Observed PRP Responses (95% CI)			
	HV PRP-T 12 µg n = 170	HV PRP-OMPC 3 µg n = 167	HV PRP-OMPC 6 µg n = 158	Pentacel® + Recombivax HB® n = 154
% ≥1.0 µg/mL	68.2% (60.7%, 75.2%)	95.8% (91.6%, 98.3%)	95.6% (91.1%, 98.2%)	80.5% (73.4%, 86.5%)
Geometric Mean Antibody Conc (µg/mL)	1.9 (1.5, 2.5)	9.9 (8.1, 12.2)	11.9 (9.7, 14.6)	3.9 (3.1, 5.0)

PRP-T = polyribosylribitol phosphate–tetanus toxoid conjugate; PRP-OMPC = PRP-*Neisseria meningitidis* outer membrane protein complex conjugate; n = number of participants with results

- PRP-OMPC-containing formulations of the HV had acceptable Hib responses; whereas, PRP-T formulation did not
- HV PRP-OMPC 3 µg and 6 µg formulations had similarly high Hib responses
  - 6 µg formulation associated with slightly higher rates of injection-site and systemic adverse events
- HV PRP-OMPC 3 µg was chosen for further development

Diaz-Mitoma et al. *Vaccine* 29 (2011) 1324–1331.

Comparison of US Combination Vaccine Schedules

Vaccines	2 months	4 months	6 months	15-18 months	Total Shots
Pediarix®*	X	X	X	Infanrix®†	7 or 8
Hib	X	X	(X)	X	
Pentacel®‡	X	X	X	X	6
HepB	X		X		
Vaxelis	X	X	X		4 or 5
Pentacel®‡				X	
Daptacel®§ + Hib				X + X	

* DTaP-HepB-IPV (GlaxoSmithKline)
† DTaP (GlaxoSmithKline)
‡ DTaP-IPV/Hib (Sanofi Pasteur)
§ DTaP (Sanofi Pasteur)
X denotes an injection

- Vaxelis regimen has 2 to 4 fewer injections than Pediarix + Hib, depending on monovalent Hib
- Vaxelis regimen has 1 to 2 fewer injections than Pentacel + HepB, depending on toddler vaccine(s)

Global Phase IIb/III Overview

Study	Endpoints and Schedules	Locations	Vaxelis / Comparator Number of Recipients
004 (IIb)	2, 4, 6 & 15 month Co-Ad PCV7* Immunogenicity	Canada	207 / 153
005	Non-inferiority 2,4,6 month Co-Ad RV5** Immunogenicity	US	981 / 484
006	Lot Consistency 2,4,6 month Co-Ad PCV13† Immunogenicity	US	2399 / 401
007	Non-inferiority 2,3,4,12 month Co-Ad MMRV¥ Immunogenicity	Germany, Finland, Belgium	610 / 605
008	Non-inferiority 2,4,11-12 month Co-Ad RV1†† Immunogenicity	Italy, Finland, Sweden	653 / 659
PRI01C	2, 3 & 4 month Co-Ad MenC§ Immunogenicity	UK	284 / 0
PRI02C	2,6 month with DTaP-IPV-Hib¶ at 4 months	Spain	384 / 0

*Prevnar7® (Pfizer); **RotaTeq® (Merck) ; †Prevnar13®(Pfizer) ; ¥ProQuad®(Merck); ††Rotarix® (GSK); §Neis-Vac-C® (Baxter AG) or Menjugate® (Novartis); ¶Pediacel® (Sanofi Pasteur)

- Across Phase IIb/III, over 5,500 Vaxelis recipients

Study 005 Design

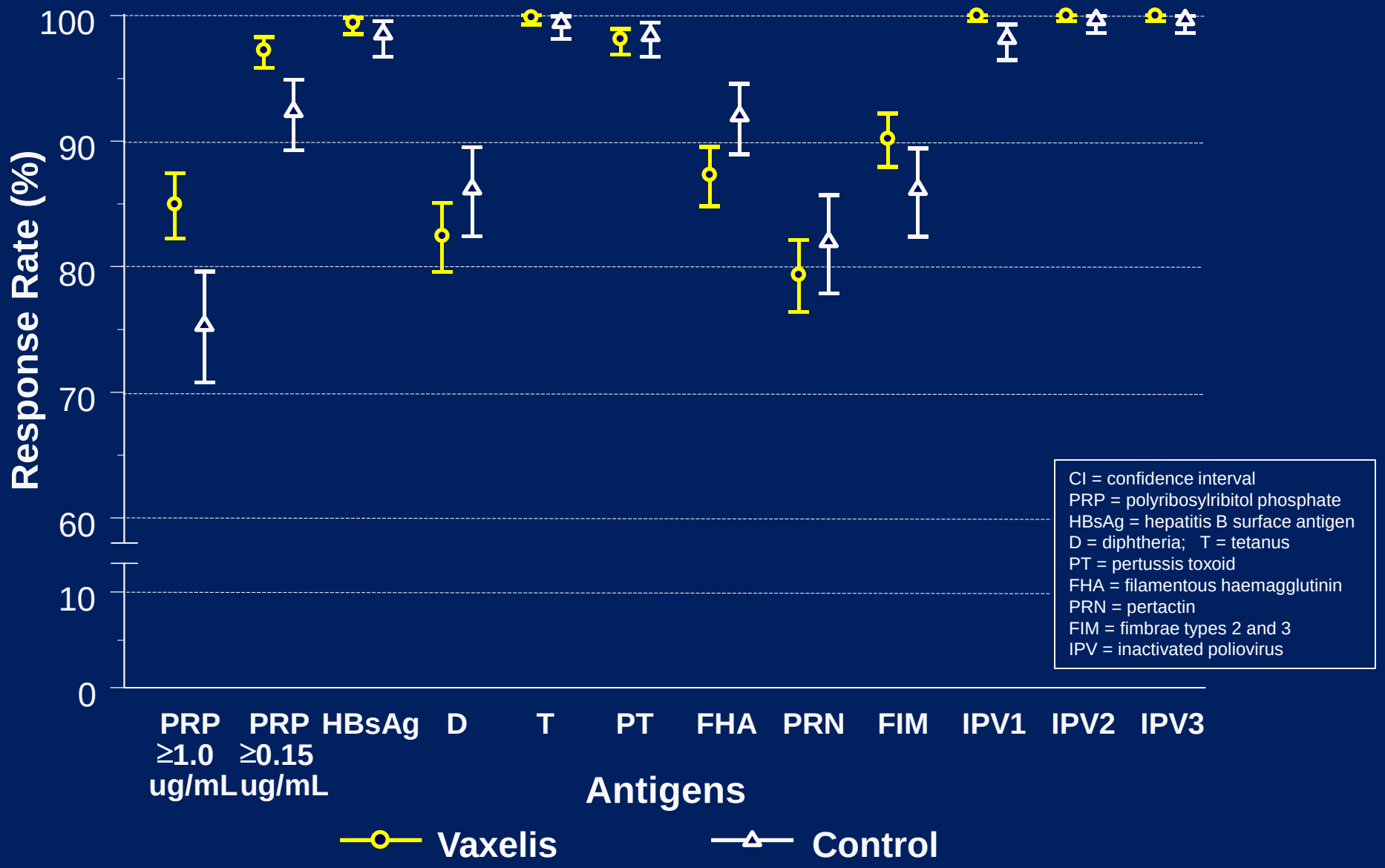
Group	Infant Series				Toddler Dose	Close-out
	2 months	4 months	6 months	7 months	15 months	16 months
1 (N=981)	*Blood Draw* Vaxelis Prevnar 13 RotaTeq	Vaxelis Prevnar 13 RotaTeq	Vaxelis Prevnar 13 RotaTeq	*Blood Draw*	*Blood Draw* Daptacel PedvaxHIB Prevnar 13	*Blood Draw*
2 (N=484)	*Blood Draw* Pentacel Recombivax HB Prevnar 13 RotaTeq	Pentacel Prevnar 13 RotaTeq	Pentacel Recombivax HB Prevnar 13 RotaTeq		*Blood Draw* Daptacel ActHIB Prevnar 13	

- Pivotal US non-inferiority to licensed component control study (Postdose 3 and Postdose 4)
- Immunogenicity of RotaTeq (Postdose 3)

Prevnar13®: Pneumococcal 13-valent Conjugate Vaccine (Pfizer); **RotaTeq®**: Rotavirus Vaccine, Live, Oral, Pentavalent (Merck)
Daptacel®: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi Pasteur); **Pedvax HIB®**: Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) (Merck); **Pentacel®**: Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine (Sanofi Pasteur); **Recombivax HB®**: Hepatitis B Vaccine (Recombinant) (Merck); **ActHIB®**: Haemophilus B conjugate vaccine (tetanus toxoid conjugate) (Sanofi Pasteur)

Marshall et al. *Pediatrics* 136 (2015) e323-332.

Study 005: Antibody Response Rates and 95% CIs at One Month Postdose 3



Study 005: Non-Inferiority Analysis of Pertussis Antibody Responses and Concentrations at One Month Postdose 3

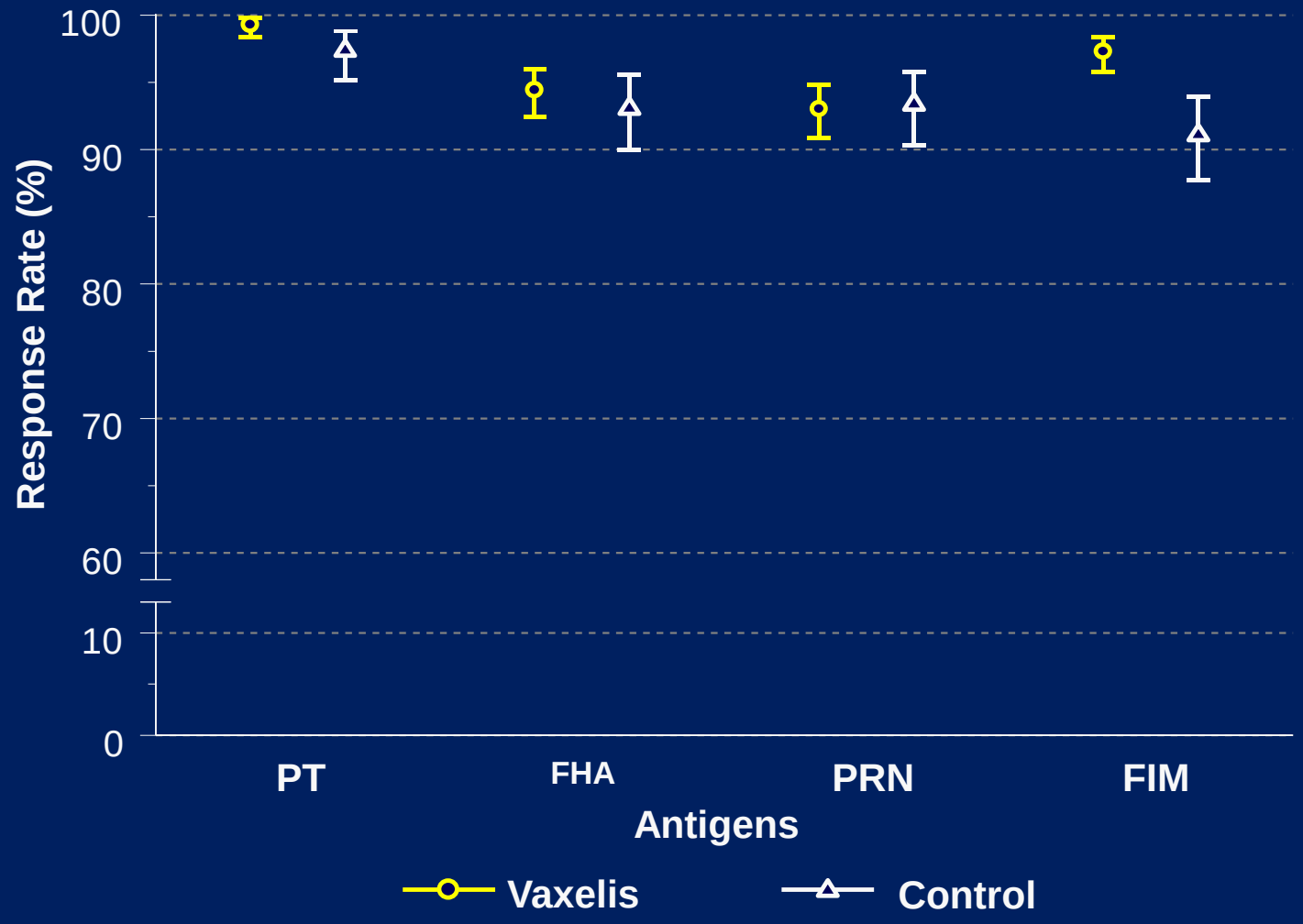
Antigen	Endpoint	Vaxelis (N = 924)		Control (N = 460)		Estimated Response Difference / GMC Ratio (95% CI)	NI Margin	Conclusion: Non-Inferiority Criterion Met / Not Met
		n	Estimated Response / GMC	n	Estimated Response / GMC			
PT	% vaccine response	796	98.1	391	98.5	-0.33 (-1.80, 1.60)	-10%	Met
	GMC	810	109.6	400	85.4	1.28 (1.20, 1.38)	0.67	Met
FHA	% vaccine response	796	87.3	391	92.0	-4.70 (-8.14, -0.97)	-10%	Met
	GMC	810	46.6	400	72.3	0.64 (0.59, 0.70)	0.67	Not Met
PRN	% vaccine response	794	79.3	390	82.0	-2.67 (-7.27, 2.23)	-10%	Met
	GMC	808	55.8	400	66.8	0.83 (0.73, 0.95)	0.67	Met
FIM	% vaccine response	796	90.2	391	86.2	4.05 (0.23, 8.28)	-10%	Met
	GMC	809	235.9	400	184.4	1.28 (1.15, 1.42)	0.67	Met

N = participants in analysis population; n = number of participants with results; GMC = geometric mean concentration; CI = confidence interval; NI = non-inferiority

The pertussis vaccine response was defined as follows: (1) if prevaccination antibody concentration was < 4X the lower limit of quantitation (LLOQ), then the postvaccination antibody concentration was ≥ 4X LLOQ; (2) if prevaccination antibody concentration was ≥ 4X LLOQ, then the postvaccination antibody concentration was ≥ prevaccination level. The prevaccination level was defined as the antibody concentration before Dose 1.

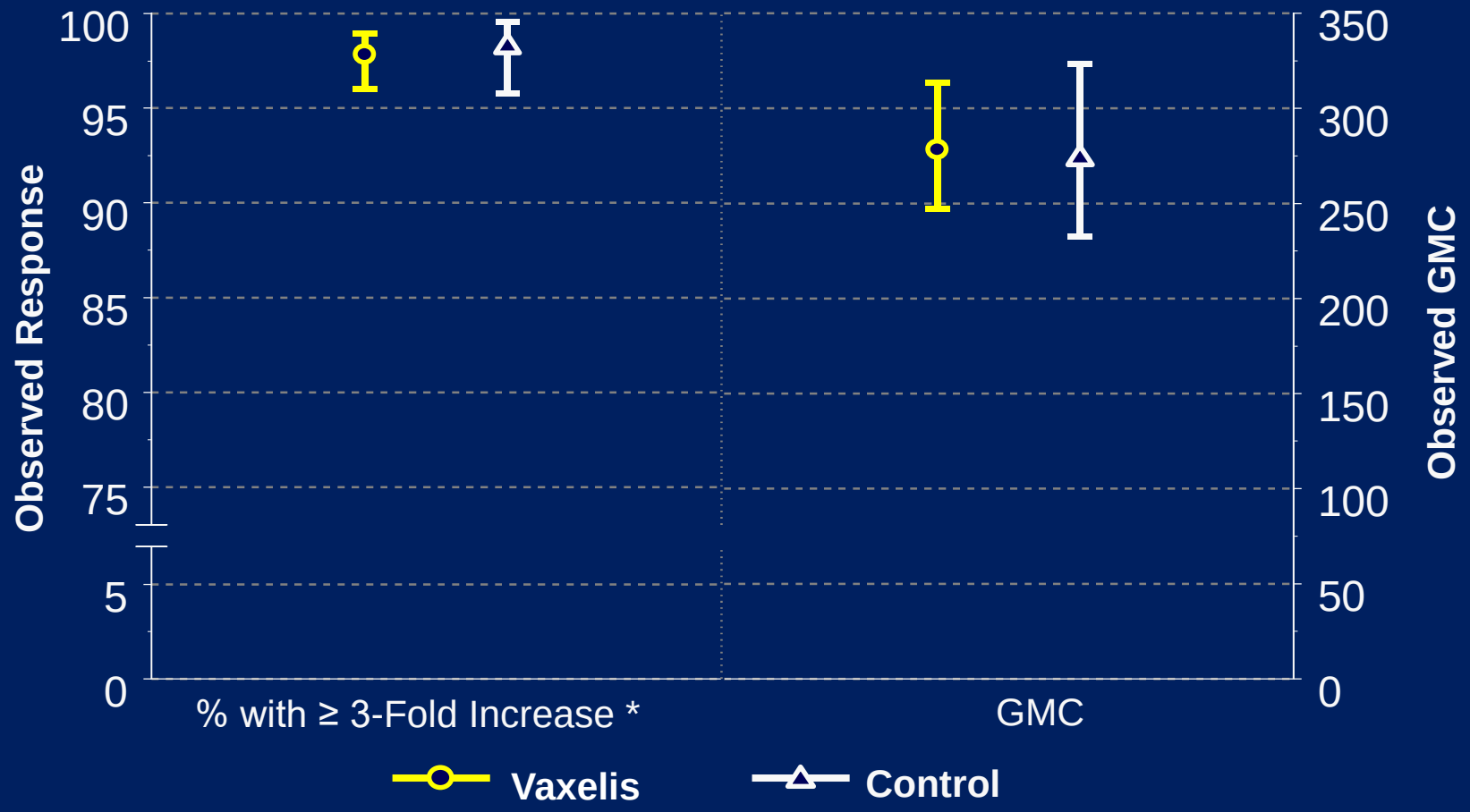
Postdose 3 non-inferiority criteria met for all pertussis antibody endpoints except FHA GMC

Study 005: Pertussis Antigen Response Rates (with 95% CIs) at One Month Post-Toddler Dose



Post-toddler dose non-inferiority criteria met for all pertussis antibody endpoints

Study 005: Summary of Serum Anti-Rotavirus IgA Responses (with 95% CI) at One Month Postdose 3



Rotavirus immunogenicity non-inferior when given with hexavalent vs control vaccines

* Increase from Baseline to Postdose 3
CI = confidence interval; GMC = geometric mean concentration

Study 006 Design

Group	Infant Series				Toddler Dose	Close-out
	2 months	4 months	6 months	7 months	15 months	16 months
1 (N=800)	*Blood Draw* Vaxelis, Lot A Prevnar 13 RotaTeq	Vaxelis, Lot A Prevnar 13 RotaTeq	Vaxelis, Lot A Prevnar 13 RotaTeq	*Blood Draw*	*Blood Draw* Pentacel Prevnar 13	*Blood Draw*
2 (N=797)	*Blood Draw* Vaxelis, Lot B Prevnar 13 RotaTeq	Vaxelis,Lot B Prevnar 13 RotaTeq	Vaxelis, Lot B Prevnar 13 RotaTeq		*Blood Draw* Pentacel Prevnar 13	
3 (N=807)	*Blood Draw* Vaxelis, Lot C Prevnar 13 RotaTeq	Vaxelis, Lot C Prevnar 13 RotaTeq	Vaxelis, Lot C Prevnar 13 RotaTeq		*Blood Draw* Pentacel Prevnar 13	
4 (N=401)	*Blood Draw* Pentacel Recombivax HB Prevnar 13 RotaTeq	Pentacel Prevnar 13 RotaTeq	Pentacel Recombivax HB Prevnar 13 RotaTeq		*Blood Draw* Pentacel Prevnar 13	

- Lot Consistency Study (Postdose 3)
  - Consistent immune responses to all antigens were shown across 3 lots
- Immunogenicity of Prevnar 13 (Postdose 3)

Block et al. *Ped Inf Dis J*. (2017) 36:202–208.

Study 006: Analysis of Postdose 3 Anti-Pneumococcal (PN) Responses

Antigen	Vaxelis (N = 2232)		Control (N = 370)		GMC Ratio (95% CI)	NI Margin	NI Criterion Met / Not Met
	n	Estimated GMC	n	Estimated GMC			
PN 1	1256	1.38	191	1.50	0.92 (0.82, 1.04)	0.67	Met
PN 3	1255	0.48	191	0.51	0.95 (0.84, 1.06)	0.67	Met
PN 4	1255	1.19	189	1.19	1.00 (0.89, 1.12)	0.67	Met
PN 5	1256	1.42	191	1.53	0.93 (0.80, 1.07)	0.67	Met
PN 6A	1251	2.52	191	2.89	0.87 (0.77, 0.99)	0.67	Met
PN 6B	1255	0.96	190	1.22	0.79 (0.64, 0.96)	0.67	Not Met
PN 7F	1256	2.68	191	3.02	0.89 (0.80, 0.99)	0.67	Met
PN 9V	1256	1.31	189	1.31	1.00 (0.88, 1.13)	0.67	Met
PN 14	1256	4.66	191	4.90	0.95 (0.82, 1.10)	0.67	Met
PN 18C	1253	1.57	191	1.78	0.89 (0.79, 1.00)	0.67	Met
PN 19A	1254	1.56	191	1.71	0.91 (0.80, 1.03)	0.67	Met
PN 19F	1256	2.14	191	2.21	0.97 (0.87, 1.08)	0.67	Met
PN 23F	1254	1.05	190	1.16	0.90 (0.77, 1.06)	0.67	Met

N = participants in analysis population; n = number of participants with results; GMC = geometric mean concentration; NI = Non-inferiority

PN 6B response missed NI study endpoint but would have satisfied Prevnar 13 NI GMC criterion (> 0.5)

Study 006: Hib Response in American Indian/Alaskan Native (AI/AN) Subset and All Races

		American Indian or Alaskan Native		All Races	
		Vaxelis	Control	Vaxelis	Control
Time Point	**Endpoint**	**Observed Response (95% CI)**	**Observed Response (95% CI)**	**Observed Response (95% CI)**	**Observed Response (95% CI)**
Pre-Vaccination 1	% with titer ≥0.15 ug/mL (s/n)	39.5 (58/147) (31.5, 47.8)	50.0 (13/26) (29.9, 70.1)	33.5 (654/1950) (31.4, 35.7)	31.6 (104/329) (26.6, 36.9)
	% with titer ≥1.0 ug/mL (s/n)	4.8 (7/147) (1.9, 9.6)	3.9 (1/26) (0.1, 19.6)	7.3 (142/1950) (6.2, 8.5)	6.7 (22/329) (4.2, 10.0)
	GMC	0.1 (0.1, 0.2)	0.2 (0.1, 0.3)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)
Postdose 3	% with titer ≥0.15 ug/mL (s/n)	100 (124/124) (97.1, 100)	100 (22/22) (84.6, 100)	98.4 (1766/1795) (97.7, 98.9)	96.2(277/288) (93.3, 98.1)
	% with titer ≥1.0 ug/mL (s/n)	92.7 (115/124) (86.7, 96.6)	86.4 (19/22) (65.1, 97.1)	87.5 (1570/1795) (85.8, 89.0)	79.5 (229/288) (74.4, 84.0)
	GMC	7.8 (6.2, 9.9)	5.9 (3.1, 11.2)	6.1 (5.6, 6.5)	3.8 (3.1, 4.6)
Post-toddler Dose	% with titer ≥0.15 ug/mL (s/n)	100 (102/102) (96.5, 100)	100(16/16) (79.4, 100)	100 (1577/1577) (99.8, 100)	100 (241/241) (98.5, 100)
	% with titer ≥1.0 ug/mL (s/n)	100 (102/102) (96.5, 100)	100(16/16) (79.4, 100)	99.6 (1570/1577) (99.1, 99.8)	97.5 (235/241) (94.7, 99.1)
	GMC	55.4 (44.4, 69.1)	20.9 (13.8, 31.5)	49.4 (46.8, 52.2)	19.2 (16.1, 22.8)

s = number of responders; n=number of subjects in category

- Similar baseline immunity and robust Postdose 3 Hib responses in AI/AN subset and overall study population
- Robust Post-toddler responses consistent with monovalent PRP-OMPC + PRP-T mixed schedule

Study 008 Design

- Double-blind, active-comparator controlled study conducted in Italy, Sweden, and Finland
- Acceptability of response rates and non-inferiority (NI) vs. Infanrix hexa (GSK)
- Superiority of Hib response rates and NI of concomitant Rotarix (GSK) tested Postdose 2
- Assessment of safety profile in 2, 4, 11-12 month schedule

Group	Subset	Infant Series			Toddler Dose	Close-out
		Visit 1 2 months	**Visit 2 4 months**	**Visit 3 5 months**	**Visit 4 11 to 12 months**	**Visit 5 12 to 13 months**
Vaxelis (N=653)	1 (n=195)	*Blood Draw* **Vaxelis** Prevenar 13 Rotarix	**Vaxelis** Prevenar 13 Rotarix	*Blood Draw*	*Blood Draw* **Vaxelis** Prevenar 13	*Blood Draw*
	2 (n =458)	*Blood Draw* **Vaxelis** Prevenar 13 RotaTeq	**Vaxelis** Prevenar 13 RotaTeq	*Blood draw* RotaTeq	*Blood Draw* **Vaxelis** Prevenar 13	*Blood Draw*
Infanrix hexa (N=659)	1 (n =199)	*Blood Draw* **Infanrix hexa** Prevenar 13 **Rotarix**	**Infanrix hexa** Prevenar 13 **Rotarix**	*Blood Draw*	*Blood Draw* **Infanrix hexa** Prevenar 13	*Blood Draw*
	2 (n =460)	*Blood Draw* **Infanrix hexa** Prevenar 13 RotaTeq	**Infanrix hexa** Prevenar 13 RotaTeq	*Blood Draw* RotaTeq	*Blood Draw* **Infanrix hexa** Prevenar 13	*Blood Draw*

Silfverdal et al. *Vaccine* (2016) 3810–3816.

Study 008: One Month Postdose 2 Hib Responses Superior to Control

Time Point	Endpoint	Vaccination Group	
		Vaxelis	Infanrix hexa
		Response (95% CI)	Response (95% CI)
One Month Postdose 2	% with titer ≥ 0.15 µg/mL (s/n)	96.6 (588/609) (94.8, 97.9)	77.9 (461/592) (74.3, 81.2)
	% with titer ≥ 1.0 µg/mL (s/n)	72.9 (444/609) (69.2, 76.4)	26.7 (158/592) (23.2, 30.5)
	GMC	2.4 (2.1, 2.7)	0.5 (0.4, 0.5)

s = number of responders; n=number of subjects in category

- Robust Postdose 2 anti-PRP responses are higher for % ≥ 0.15, 1.0, and GMC as compared to PRP-T containing hexavalent vaccine
  - Statistically significant difference for % ≥ 1.0 mcg/mL demonstrated superiority
- Results consistent with Hib monovalent vaccine literature showing more rapid kinetics of PRP-OMPC response as compared to PRP-T vaccines

Study 008: All Hib Responses

Time Point	Endpoint	Vaccination Group	
		Vaxelis	Infanrix hexa
		Response (95% CI)	Response (95% CI)
One Month Postdose 2	% with titer ≥ 0.15 µg/mL (s/n)	96.6 (588/609) (94.8, 97.9)	77.9 (461/592) (74.3, 81.2)
	% with titer ≥ 1.0 µg/mL (s/n)	72.9 (444/609) (69.2, 76.4)	26.7 (158/592) (23.2, 30.5)
	GMC	2.4 (2.1, 2.7)	0.5 (0.4, 0.5)
Pre-Toddler Dose	% with titer ≥ 0.15 µg/mL (s/n)	91.4 (542/593) (88.9, 93.5)	48.1 (275/572) (43.9, 52.3)
	% with titer ≥ 1.0 µg/mL (s/n)	50.1 (297/593) (46.0, 54.2)	10.3 (59/572) (8.0, 13.1)
	GMC	0.9 (0.9, 1.0)	0.2 (0.2, 0.2)
One Month After the Toddler Dose	% with titer ≥ 0.15 µg/mL (s/n)	99.6 (452/454) (98.4, 100)	99.4 (475/478) (98.2, 99.9)
	% with titer ≥ 1.0 µg/mL (s/n)	89.9 (408/454) (86.7, 92.5)	91.0 (435/478) (88.1, 93.4)
	GMC	4.4 (4.0, 4.9)	7.8 (6.8, 8.9)

s = number of responders; n=number of subjects in category

Hib responses for Vaxelis administered at 2,4, 11-12 months are robust at all timepoints

Silfverdal et al, *Vaccine* (2016) 3810–3816.

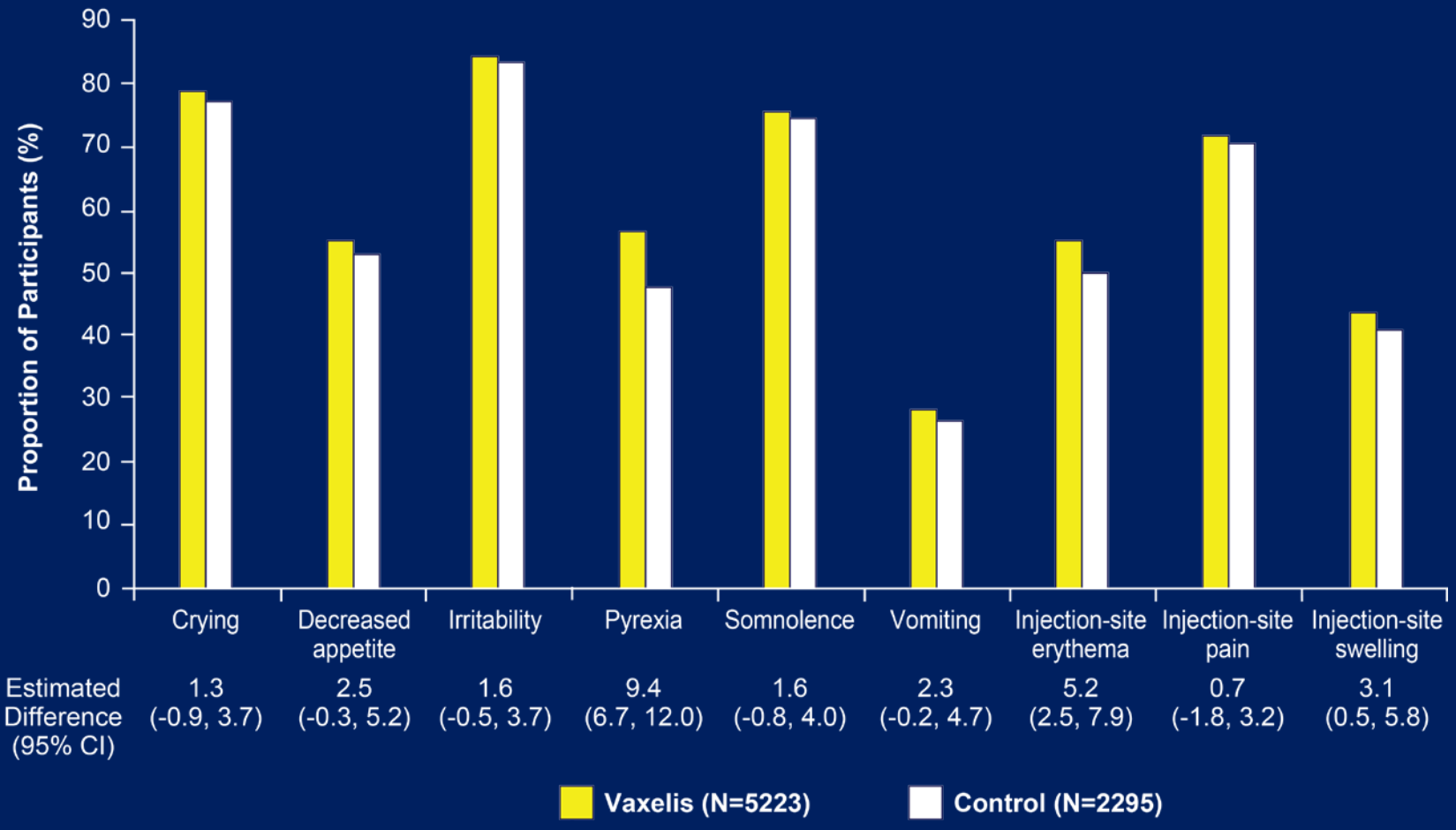
Safety Measurements for Phase III Studies

- Daily temperature measurements for 5 days after each vaccination
  - Day of vaccination counted as Day 1

38.0 ≤ Mild ≤ 38.4°C	100.4 ≤ Mild ≤ 101.1°F
38.5 ≤ Moderate ≤ 39.4°C	101.3 ≤ Moderate ≤ 102.9°F
Severe ≥ 39.5°C	Severe ≥ 103.1°F

- Solicited adverse events (AEs) for 5 days after each vaccination
  - Solicited systemic AEs: fever, vomiting, crying abnormal, drowsiness, appetite loss, irritability
  - Solicited injection-site AEs: redness, swelling, and pain/tenderness
- Unsolicited AEs for 15 days after each vaccination
- All serious adverse events from start to ~180 days (~6 months) after infant vaccination series in US and for 15 days after each vaccination in EU
- Deaths and vaccine-related serious adverse events at any time during the study

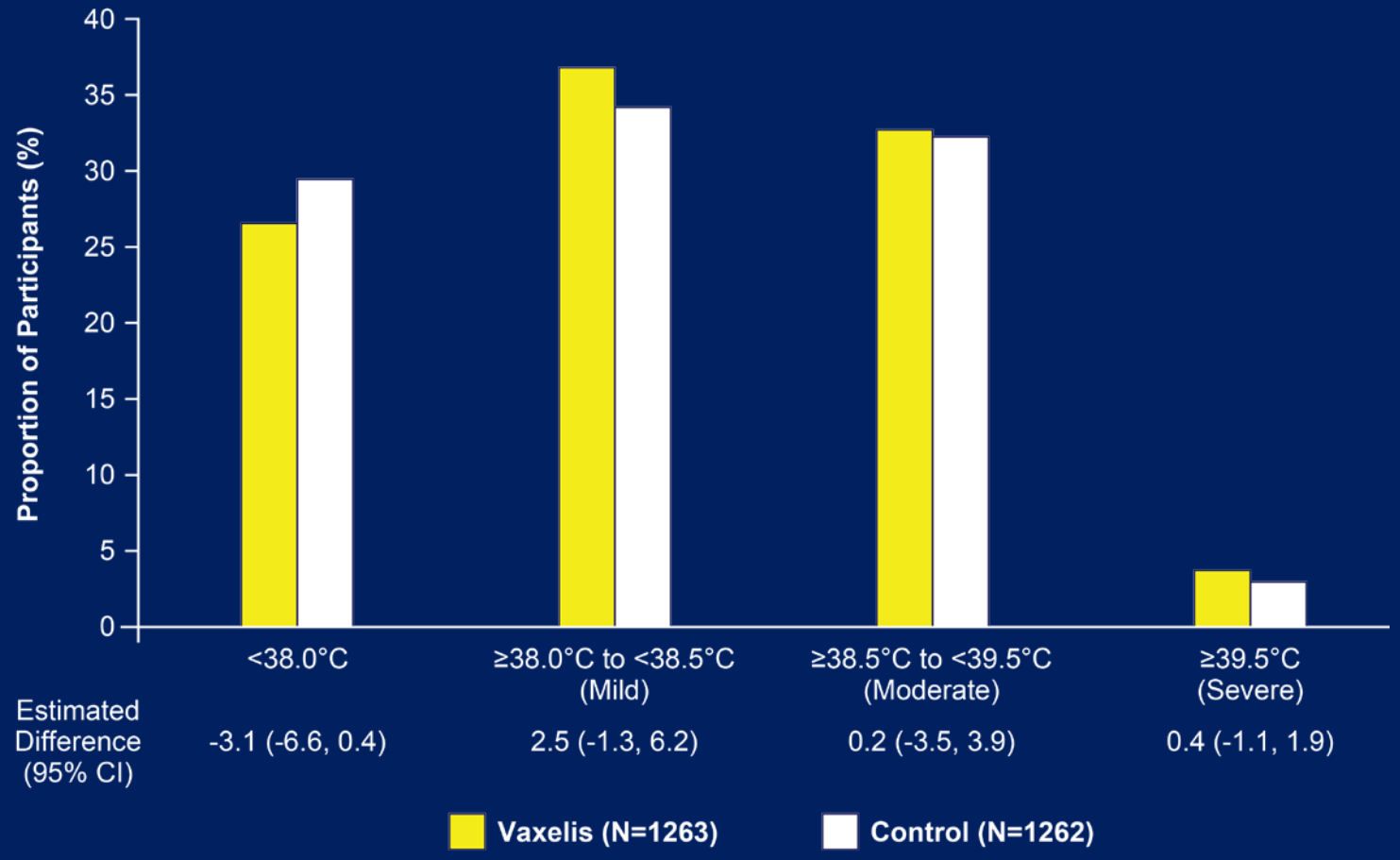
Integrated Safety Results for Vaxelis: Solicited Systemic Reactions Day 1 Through Day 5 Following Any Dose (004, 005, 006, 007, 008, 011)



- Most solicited systemic reaction incidences were similar between Vaxelis and Control, except pyrexia appeared slightly higher.

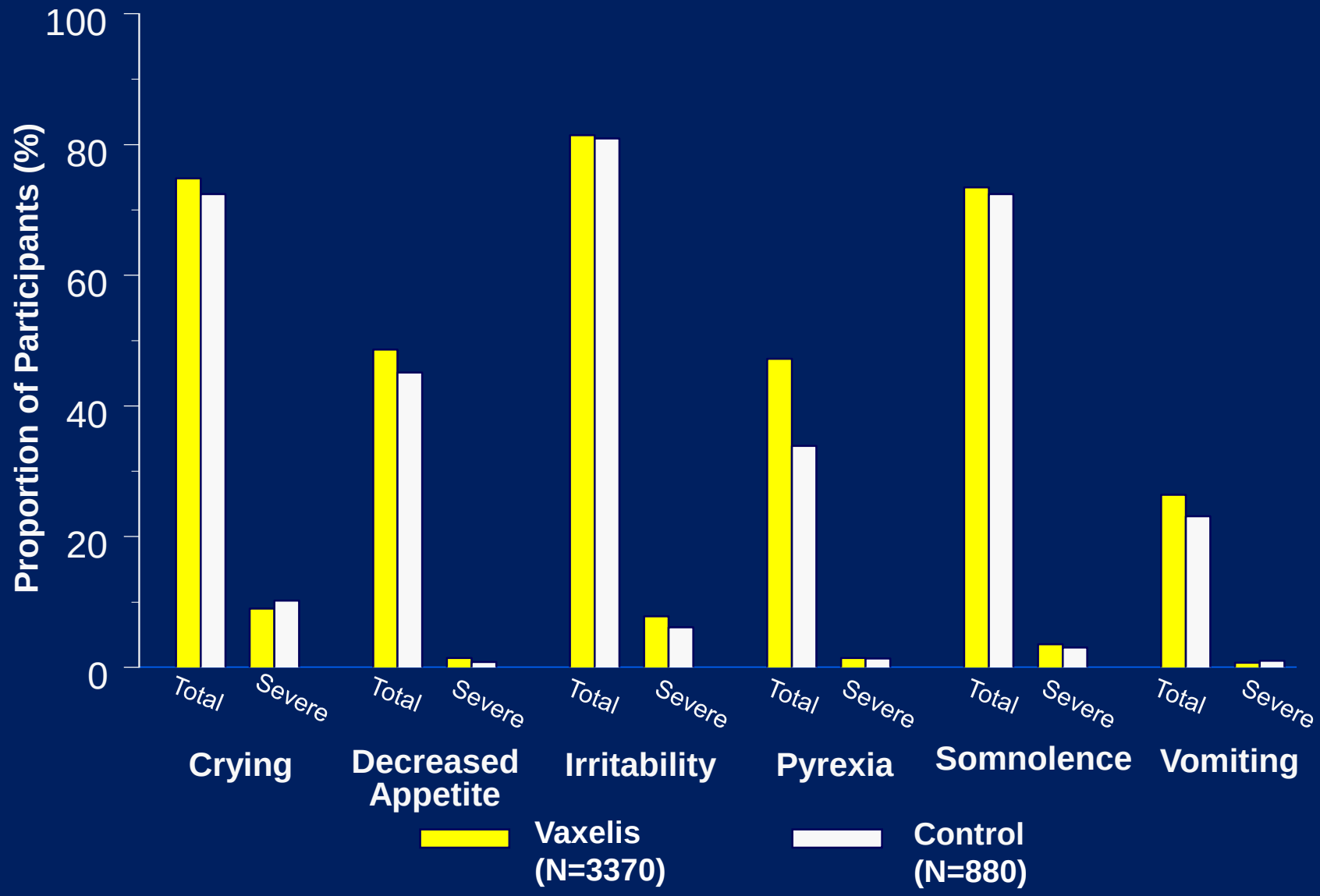
Xu et al., *PIDJ (*2018*) Publish Ahead of Print*

Integrated Safety Results for Vaxelis: Temperatures Day 1 Through Day 5 Following Any Dose, Hexavalent Control (007, 008)



- In studies with a hexavalent vaccine control, Vaxelis fever rates were similar

Studies 005 and 006 Combined: Solicited Systemic Adverse Events Day 1 Through Day 5 Following Any Infant Dose



Studies 005 and 006 Combined: Summary of Participants With Fever by Severity Day 1 Through Day 5 Following Any Infant Dose

	Vaxelis N = 3370		Control N = 880		Difference*	
	n	(%)	n	(%)	Estimate	(95% CI)
Participants with temperature data	3257	(96.6)	848	(96.4)	4105	(96.6)
Participants with no temperature data	113	(3.4)	32	(3.6)	145	(3.4)
Maximum Temperature (All Routes†)						
< 38.0°C	1658	(50.9)	546	(64.4)	-13.5	(-17.4, -9.6)
≥ 38.0°C and < 38.5 °C (Mild)	858	(26.2)	178	(21.9)	4.3	(0.8, 7.6)
≥ 38.5°C and < 39.5 °C (Moderate)	666	(20.6)	114	(12.5)	8.2	(5.2, 10.8)
≥ 39.5°C (Severe)	75	(2.3)	10	(1.2)	1.1	(-0.1, 1.9)

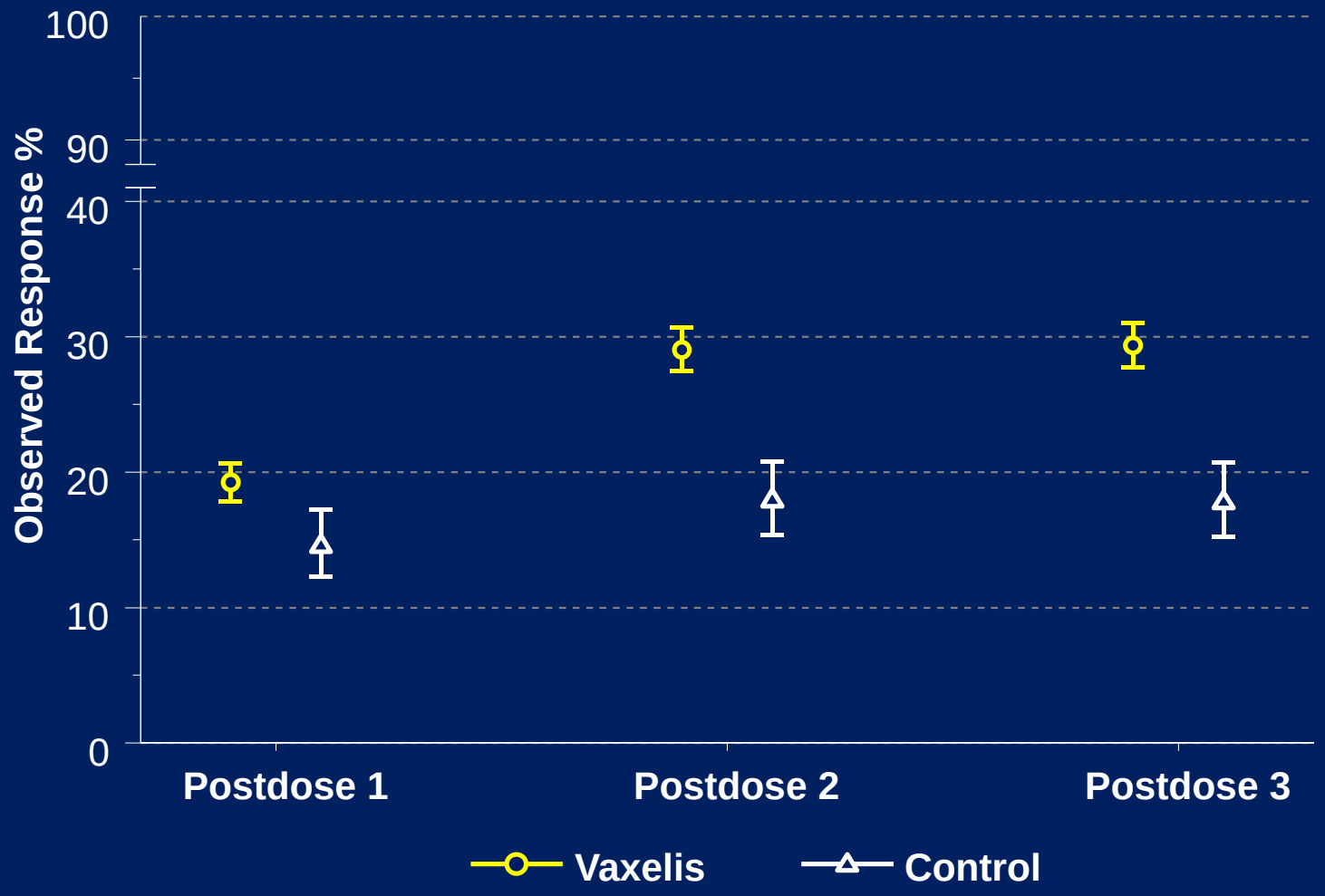
* Difference was Hexavalent group minus Control group. Estimated rate and difference were based on Miettinen and Nurminen method stratified by studies.

† Temperatures were those actually recorded, with no adjustments to the measurement route; > 90% of temperature measurements were by the rectal route.

N = number of participants in arms of combined studies; n = number of participants with results; CI = confidence interval

- Statistically significant differences in overall, mild, and moderate temperature elevations
- No significant difference observed in severe temperature elevations
- Vast majority of temperature elevations were 2 days or less in duration

Studies 005 and 006 Combined: Summary of Participants With Fever ≥ 38°C by Dose Day 1 Through Day 5 Following Each Infant Dose



Studies 005 and 006 Combined: Pyrexia, Febrile Convulsion, Convulsion Following Any Infant Dose

	Vaxelis N = 3370 n (%)	Control N = 880 n (%)
Adverse Events (Days 1 thru 15)		
Pyrexia	1627 (48.3)	310 (35.2)
Febrile convulsion	0 (0.0)	0 (0.0)
Convulsion	0 (0.0)	0 (0.0)
Serious Adverse Events (SAE) (Days 1 thru 15)		
Pyrexia	3 (0.1)	0 (0.0)
Febrile convulsion	0 (0.0)	0 (0.0)
Convulsion	0 (0.0)	0 (0.0)
Serious Adverse Events (Days 1 thru 181*)		
Pyrexia	4 (0.1)	1 (0.1)
Febrile convulsion†	5 (0.1)	0 (0.0)
Convulsion†	1 (0.0)	2 (0.2)

* Covers period from 1st infant vaccination through day 181 after 3rd vaccination.

† SAEs of febrile convulsion and convulsion occurred outside of 15-day safety follow-up period and were considered by investigator to be unrelated to study vaccines.

N = number of participants in arms of combined studies; n = number of participants with results

- Low and similar incidence of pyrexia SAEs for Vaxelis and Control vaccines
- No febrile seizures within 15 days of vaccination

Studies 005 and 006 Combined: Summary of Participants With Serious Vaccine-Related Adverse Events and Who Discontinued Due to an Adverse Event

	Vaxelis N = 3370		Control N = 880		Difference*	
	n	(%)	n	(%)	Estimate	(95 % CI)
Number and percentage of participants:						
With serious vaccine-related adverse events	6	(0.2)	0	(0.0)	0.2	(-0.4, 0.4)
Who died (none were vaccine-related)	6	(0.2)	1	(0.1)	0.1	(-0.5, 0.3)
Discontinued due to an adverse event	8	(0.2)	1	(0.1)	0.2	(-0.4, 0.4)
Discontinued due to a vaccine-related adverse event	2	(0.1)	1	(0.1)	0.0	(-0.6, 0.2)
Discontinued due to a serious adverse event	3	(0.1)	0	(0.0)	0.1	(-0.4, 0.3)
Discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0.0	(-0.5, 0.1)

* Difference was Hexavalent group minus Control group

N = number of participants in arms of combined studies; n = number of participants with results; CI = confidence interval

- Low incidence of vaccine-related serious adverse events and study discontinuations due to adverse events in both vaccination groups

Clinical Summary

- Vaxelis was evaluated in 6 Phase III clinical studies, in which a total of over 5,000 infants 6 to 12 weeks of age at enrollment received at least 1 dose of Vaxelis.

- Two of these (studies 005 and 006) were controlled clinical studies conducted in the US, in which a total of 3,380 infants 6 to 12 weeks of age at enrollment received at least 1 dose of Vaxelis.

- In these studies, Vaxelis demonstrated robust immunogenicity and an acceptable safety profile consistent with its component vaccines.

Overall Status and Summary

- Combination vaccines improve vaccination compliance and timeliness.
- Hexavalent vaccines have been used outside the US for many years.
- Vaxelis already administered in EU
  - Vaxelis was licensed in EU in February 2016, launched in May 2017
  - Commercially available in 5 EU countries
  - Over 1.5 million doses distributed; ongoing pharmacovigilance shows no unexpected safety signals
- Vaxelis approved by US FDA on December 21, 2018
  - The Merck-Sanofi Pasteur Joint Venture is building up supply for US launch
- Vaxelis will provide a new option for meeting the recommended US vaccination schedule with fewer injections.